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Editorial

Personalizing Permissive Hypercapnia in Acute Severe Respiratory Failure

Hypercapnia with or without acidemia is common in critically ill patients receiving invasive mechanical ventilation and its management often poses a clinical challenge.¹ Patients receiving invasive ventilation are at risk of developing ventilator-induced lung injury and current guidelines recommend a volume- and pressure-limited strategy (lung-protective ventilation), shown to confer mortality benefit in acute respiratory distress syndrome (ARDS).^{2,3} Permissive hypercapnia with or without acidemia has been adopted as a strategy to facilitate low tidal volume protective ventilation and minimize ventilator-induced lung injury.⁴ Certain subsets of patients, such as those with evidence of right ventricular injury and acute brain injury, however, may not tolerate the systemic effects of hypercapnia, making this strategy potentially harmful.⁴ As a result, bedside clinicians are often faced with opposing treatment objectives: lung protection at the expense of potential worsening of extrapulmonary organ injuries or a different approach that may mitigate the adverse physiological effects of hypercapnia? In this Editorial, we discuss the mechanisms of hypercapnia in invasively ventilated patients, the evidence pertaining to the effects of hypercapnia on clinical outcomes and the systemic physiological effects of hypercapnia with a focus on pulmonary and cerebral circulation. We propose a personalized approach for high-risk patients in whom permissive hypercapnia may be contraindicated as a lung-protective strategy.

Mechanisms of Hypercapnia in Respiratory Failure Requiring Invasive Mechanical Ventilation

Hypercapnia may occur in the context of acute respiratory failure of any etiology, including infiltrative lung injury (eg, ARDS) and reactive airways disease with dynamic hyperinflation (eg, asthma).^{1,5} Alveolar hypoventilation, increased dead space and ventilation/perfusion mismatch are the mechanisms of hypercapnia in early ARDS, likely caused by pulmonary microthrombosis and dysregulated lung inflammation.⁶ In late ARDS, structural changes caused by advanced alveolar fibroproliferative processes leading to reduced pulmonary compliance are the likely mechanisms of hypercapnia.⁷ In acute

severe airflow limitation (eg, life-threatening asthma), dynamic hyperinflation results in increased dead space ventilation and hypercapnia.⁵ In patients with reduced lung compliance, a low tidal volume (6 mL/kg of predicted body weight) approach results in decreased minute ventilation and hypercapnia due to reduced carbon dioxide (CO₂) clearance.^{3,4}

Effect of Hypercapnia on Patient-centered Outcomes

There is a lack of large-scale randomized data on the effect of hypercapnia on clinical outcomes; nevertheless, permissive hypercapnia is being used as part of a lung-protective ventilation strategy. In a recent meta-analysis that included 26 observational and three small sample size randomized studies (10,101 patients in total), patients with hypercapnia receiving lung-protective ventilation were found to have lower mortality compared to normocapnic patients receiving non-protective ventilation.⁸ Studies comparing patients with hypercapnia receiving lung-protective ventilation with normocapnic patients also receiving lung-protective ventilation reported higher mortality in the former group.⁸ It remains, however, unclear how different pH and hypercapnia thresholds may affect patient-centered outcomes, making a mechanistic interpretation of the relevant literature challenging.^{8,9} It could be posited that the degree of hypercapnia, reflecting disease severity (lung injury or airway inflammation) combined with the systemic effects of hypercapnia and respiratory acidemia, may explain the observed adverse outcomes.^{8,9} In a secondary analysis of three prospective noninterventional cohort studies (1,899 patients) and after multiple adjustments and propensity analysis, Nin et al¹⁰ found that severe hypercapnia (defined as partial pressure of arterial CO₂ [P_aCO₂] of >50 mmHg) was an independent predictor of intensive care unit mortality. These patients also exhibited higher rates of organ dysfunction and experienced more complications during invasive mechanical ventilation, particularly those with moderate to severe ARDS.¹⁰ It should be noted that more than 50% of the patients studied were cases from 1998 to 2004 and lung-protective ventilation was not used according to latest standards (higher driving pressure cutoffs, usually no ventilator adjustments made



according to transpulmonary pressures [not routinely measured], and respiratory rate and mechanical power not necessarily been taken into account), which questions the validity of the conclusions.¹⁰ A subgroup analysis of the international multicenter Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study, which included 2,813 patients with ARDS, found no independent association (positive or negative) between hypercapnia and clinical outcomes.¹¹

Overall, outcome effects are derived by association from large epidemiological datasets mainly in ARDS patient populations or meta-analytic data, and therefore are subject to inherent bias despite statistical corrections. Understanding of the clinically important end-organ effects may, therefore, inform individualized management of hypercapnia until large-scale randomized evidence emerges.

Clinically Significant Physiological Effects of Hypercapnia During Invasive Mechanical Ventilation

Right Ventricle and Pulmonary Circulation

Hypercapnia causes pulmonary arterial vasoconstriction and an acute increase in pulmonary artery pressure and right ventricular afterload.^{12,13} The intrinsic right ventricular contractile force increases to compensate for the elevated right ventricular afterload (homeometric adaptation) and the right ventricle may dilate (heterometric adaptation) to maintain flow.^{14,15} These changes in right ventricular biomechanics may affect the interplay between the right ventricle and pulmonary artery (right ventricle–pulmonary artery coupling), causing a negative diastolic interaction between the right and left ventricles, leading to systemic venous congestion, impaired left ventricular filling, coronary hypoperfusion and shock.^{12–14} In ARDS, hypercapnia without acidemia has been identified as a risk factor for right ventricular dilatation with paradoxical septal motion, which is an independent risk factor for mortality.¹⁵ The hemodynamic effects of hypercapnia, and resultant secondary organ injuries, may in part explain the increased mortality observed across studies despite lung-protective ventilation.^{8,10,13,15} In patients with evidence of right ventricular injury (dilatation and/or dysfunction and/or failure) in the context of ARDS, in whom adequate CO₂ clearance using lung-protective settings is not possible, a permissive hypercapnia strategy may worsen systemic arterial and venous hemodynamics. In the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, patients with hypercapnic acidemia and elevated ventilatory pressures despite lung-protective ventilation randomly allocated to extracorporeal membrane oxygenation (ECMO), had the greatest survival benefit.¹⁶ This finding may indicate that ECMO confers outcome benefits by mitigating not only ventilator-induced lung injury, but also the adverse effects of hypercapnia on pulmonary vasculature and the right ventricle.^{13,15,16} This hypothesis is supported further by recent observational data suggesting that patient phenotypes with ARDS and evidence of right ventricular injury on echocardiography, may be a specific target for respiratory ECMO.¹⁷

Cerebral Circulation

Hypercapnia may affect cerebrovascular contractility independently or in association with respiratory acidemia, causing cerebral vasodilatation and increased cerebral blood flow.^{4,18} The hyperperfusion effect of elevated CO₂ may result in increased intracranial pressure and cerebral edema.^{4,18} Patients with acute brain injury (defined as traumatic brain injury, intracranial hemorrhage or ischemic stroke) may require invasive mechanical ventilation and develop acute severe respiratory failure due to parenchymal lung injury (eg, ventilator-associated pneumonia, aspiration pneumonitis, pulmonary contusions leading to ARDS) or airway inflammation and bronchospasm.¹⁹ Permissive hypercapnia in these patients may have deleterious neurological consequences, but there is currently a lack of data reporting on neurological mechanistic or clinical outcomes in patients with acute brain injury (with or without elevated intracranial pressure) and hypercapnic respiratory failure subjected to different degrees of permissive hypercapnia as part of a lung-protective strategy.²⁰ However, the significance of the rate of reduction of P_aCO₂ in patients with acute hypercapnic acidemia (defined as a pH of <7.3 and P_aCO₂ of >50 mmHg) requiring respiratory ECMO, has been addressed in a large multicenter registry study.²¹ A rapid reduction in P_aCO₂ (>50%) within the first 24 hours of ECMO application or a decrease of more than 27 mmHg, is associated independently with an increased risk of intracranial hemorrhage.^{21,22} This finding underscores the impact disrupted CO₂ homeostasis and abrupt changes in cerebrospinal fluid pH may have on clinical outcomes. The postulated mechanism of neurological injury in hypercapnic patients with acute decreases in P_aCO₂ levels is acute alkalization of the cerebrospinal fluid, leading to cerebral vasoconstriction and increased neuronal excitability, which result in decreased cerebral blood flow and increased metabolic demand respectively.^{21–23} Therefore, a gradual correction of hypercapnia is recommended in invasively ventilated patients requiring ECMO for refractory hypercapnia despite lung-protective ventilation.^{21–23}

Other Organ Systems

In preclinical studies, hypercapnic acidemia has been shown to adversely affect lung epithelial cell repair, pulmonary and renal vasculature, and diaphragmatic and skeletal myogenic tone.⁴ The clinically relevant consequences of permissive hypercapnia on organ systems (eg, systemic circulation, renal physiology, and immunological responses), however, are yet to be determined in clinical studies.⁴

Management of Acute Severe Hypercapnic Respiratory Failure

In the absence of a high level of evidence, it would be plausible to institute a personalized physiologically driven management strategy that takes into account the cause of respiratory failure (ARDS or acute life-threatening obstructive

respiratory disease) and associated conditions, such as right ventricular injury and acute brain injury, where hypercapnic acidemia can be potentially harmful. This approach would involve adherence to a lung-protective strategy with prompt consideration of adjunctive therapies, such as prone positioning and escalation to mechanical cardiorespiratory support (where appropriate), in cases of hypercapnic acidemia refractory to conventional management.

Based on current recommendations, lung-protective ventilation comprises low tidal volume (4–8 mL/kg of predicted body weight) and plateau pressure (<30 cmH₂O) combined with prone positioning when appropriate.² In ARDS, prone positioning may reduce alveolar dead space by increasing alveolar recruitment leading to a decrease in $P_a\text{CO}_2$.⁴ The merits of limiting driving pressure (plateau pressure – total positive-end expiratory pressure) and mechanical power, normalizing elastance to predicted body weight, positive-end expiratory pressure optimization, diaphragm protection and use of neuromuscular blockade as part of a lung-protective approach, require further prospective research.²

In severe obstructive airway disease with acute dynamic hyperinflation, the goal during invasive ventilation is to limit hyperinflation by reducing minute ventilation and prolonging

expiratory time.⁵ Measurement of end-inspiratory lung volume is the gold standard technique to quantify the degree of dynamic hyperinflation.²⁴ In clinical practice, however, end-inspiratory lung volume may be challenging to measure; however, the plateau pressure is a reasonable surrogate that can be used instead.^{5,24} The application of low level of external positive-end expiratory pressure may be considered with close monitoring of the effect it may have on plateau pressure.⁵

Respiratory or cardiorespiratory ECMO (venovenous, venovenous arterial, or venopulmonary) may have a role in selected cases of hypercapnic acidemia refractory to lung-protective ventilation, particularly where permissive hypercapnia may be contraindicated (eg in right ventricular injury, brain injury). Use of extracorporeal CO₂ removal remains a research indication and should be avoided outside clinical trials.²

A proposed algorithm providing more details on individualized management of hypercapnia is described in Figure 1.

Conclusions

Hypercapnic acidemia during lung-protective ventilation may have significant cardiovascular and neurological consequences, and perhaps it should not be a ventilatory goal per se,

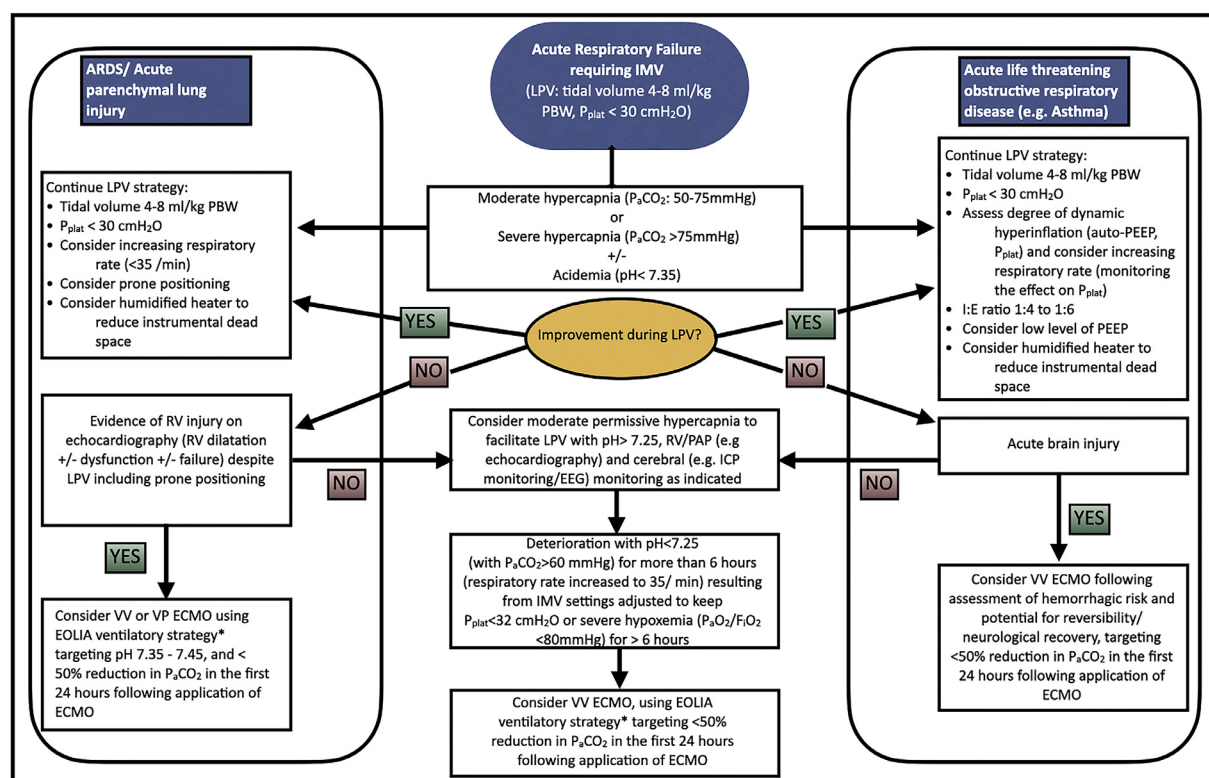


Figure 1. Proposed algorithm for the management of hypercapnia in invasively ventilated patients with severe respiratory failure. It should be noted that the proposed personalized strategies in patients with end-organ effect of hypercapnic acidemia should be validated in randomized studies. *EOLIA ventilatory strategy: assist-control ventilation (ACV) mode with tidal volume to a obtain plateau pressure of 24 cmH₂O or less, PEEP of 10 cmH₂O or greater, respiratory rate of 10 to 30 /min, fraction of inspired oxygen 0.3 or airway pressure release ventilation (APRV) mode with high pressure of 24 cmH₂O or less, low pressure of 10 cmH₂O or greater, and fraction of inspired oxygen of 0.3.¹⁶ ARDS, acute respiratory distress syndrome; auto-PEEP, auto- positive end-expiratory pressure; CO₂ carbon dioxide; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalogram; EOLIA, ECMO to rescue lung injury in severe ARDS; I:E ratio, inspiratory-to-expiratory ratio; ICP, intracranial pressure; IMV, invasive mechanical ventilation; LPV, lung-protective ventilation; $P_a\text{CO}_2$, partial pressure of carbon dioxide in the arterial blood; PAP, pulmonary artery pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{plat} , plateau airway pressure; RV, right ventricle; VV ECMO, venovenous extracorporeal membrane oxygenation; VP ECMO, venopulmonary extracorporeal membrane oxygenation.

but rather prompt early consideration of adjunctive therapies (Figure 1).² However, it is currently unclear whether poor outcomes in patients with hypercapnia in the context of lung-protective ventilation reflect severity of the underlying lung damage, or the extent of hypercapnia itself, bringing about cardiovascular and cerebral vascular consequences, and organ dysfunction. Whether we should target P_aCO_2 , pH or both and their safe thresholds in critical illness, remains uncertain too. Adequately powered randomized studies comparing permissive hypercapnic acidemia during lung-protective ventilation with lung-protective strategies combined with adjunctive therapies to achieve normocapnia are needed.

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Declaration of competing interest

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